

Hacking the Brain: Dimensions of Cognitive Enhancement

Martin Dresler,^{*,†,‡} Anders Sandberg,[‡] Christoph Bublitz,[§] Kathrin Ohla,^{||} Carlos Trenado,^{⊥,‡} Aleksandra Mroczko-Wąsowicz,[▽] Simone Kühn,^{○,◆} and Dimitris Repantis[¶]

[†]Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Centre, Nijmegen 6525 EN, The Netherlands

[‡]Future of Humanity Institute, Oxford University, Oxford OX1 1PT, United Kingdom

[§]Faculty of Law, University of Hamburg, Hamburg 20148, Germany

^{||}Institute of Neuroscience and Medicine, Cognitive Neuroscience (INM3), Forschungszentrum Jülich, Jülich 52428, Germany

[⊥]Institute of Clinical Neuroscience and Medical Psychology, Heinrich Heine University Düsseldorf, Düsseldorf 40225, Germany

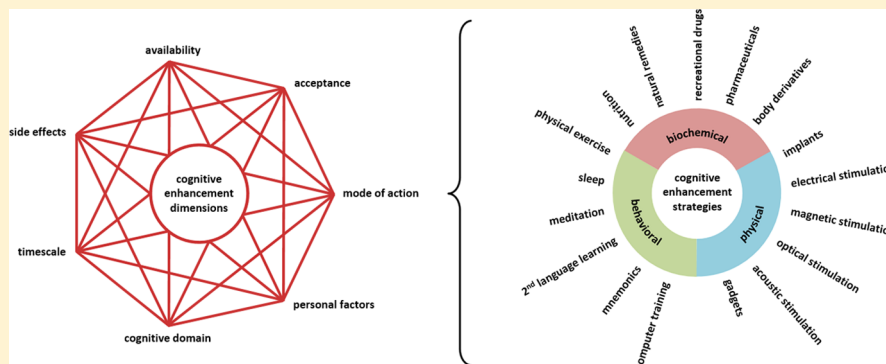
[#]Department of Psychology and Neurosciences, Leibniz Research Centre for Working Environment and Human Factors, TU Dortmund, Dortmund 44139, Germany

[▽]Institute of Philosophy of Mind and Cognition, National Yang-Ming University, Taipei 112, Taiwan

[○]Max Planck Institute for Human Development, Berlin 14195, Germany

[◆]Department of Psychiatry and Psychotherapy, University Clinic Hamburg Eppendorf, Hamburg 20246, Germany

[¶]Department of Psychiatry and Psychotherapy, Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin 12203, Germany



ABSTRACT: In an increasingly complex information society, demands for cognitive functioning are growing steadily. In recent years, numerous strategies to augment brain function have been proposed. Evidence for their efficacy (or lack thereof) and side effects has prompted discussions about ethical, societal, and medical implications. In the public debate, cognitive enhancement is often seen as a monolithic phenomenon. On a closer look, however, cognitive enhancement turns out to be a multifaceted concept: There is not one cognitive enhancer that augments brain function per se, but a great variety of interventions that can be clustered into biochemical, physical, and behavioral enhancement strategies. These cognitive enhancers differ in their mode of action, the cognitive domain they target, the time scale they work on, their availability and side effects, and how they differentially affect different groups of subjects. Here we disentangle the dimensions of cognitive enhancement, review prominent examples of cognitive enhancers that differ across these dimensions, and thereby provide a framework for both theoretical discussions and empirical research.

KEYWORDS: Neuroenhancement, brain hacking, neuroethics, cognition, memory, working memory, attention, creativity

1. INTRODUCTION

An increasingly complex world exerts increasing demands on cognitive functions—functions that evolved for a fundamentally different environment. Daily life in an information society and a postindustrial economy require cognitive skills that have to be acquired through slow, effortful, and expensive processes of education and training. Likewise, these skills can become obsolete as the world changes ever faster or be lost by the processes of aging. People also vary in their mental abilities,

allowing them to acquire certain skills more quickly or slower, which may have significant effects on life outcomes. Strategies to improve the acquisition and maintenance of cognitive skills are thus increasingly important on both an individual and societal level. These challenges of our times have fostered the

Received: October 23, 2018

Accepted: December 14, 2018

Published: December 14, 2018

exploration of strategies to enhance human brain function. While people have since time immemorial sought to improve their performance, the present era is unique in that not only the challenges are growing rapidly but so are technologies that promise to meet them. Just like the hacking culture in the realm of computer software and hardware, an increasing number of individuals experiment with strategies to creatively overcome the natural limitations of human cognitive capacity—in other words, to hack brain function. This development has led to both enthusiasm and dread, as observers have sharply differing intuitions about the feasibility, utility, risks, and eventual impact of enhancement technologies on the world.

One reason for the often polarized debates has been the lack of hard evidence. Without empirical findings, it is easy to maintain any position, as well as regard opponents as having unfounded views. A further essential source of disagreement and theoretical confusion is a tendency to view enhancement as a unitary phenomenon to be judged as a whole, rather than as a broad set of techniques with important differences and diverging implications. Only on the basis of a clear picture on how a particular enhancement strategy might affect specific cognitive processes in specific populations, along with side effects and costs to be expected, an informed theoretical debate can evolve and a promising empirical research designs to test the strategy can be proposed. In the following, we aim to elucidate seven essential dimension of cognitive enhancement, namely, (a) its mode of action, (b) the cognitive domain targeted, (c) personal factors, (d) its time scale, (e) side effects, (f) availability, and (g) social acceptance (see Figure 1). Further, we will review empirical data of prominent examples of cognitive enhancers that differ across these dimensions and thereby illustrate some of their nuanced implications. The aim of our Review is to sketch a general framework that will foster both theoretical discussions and empirical research.

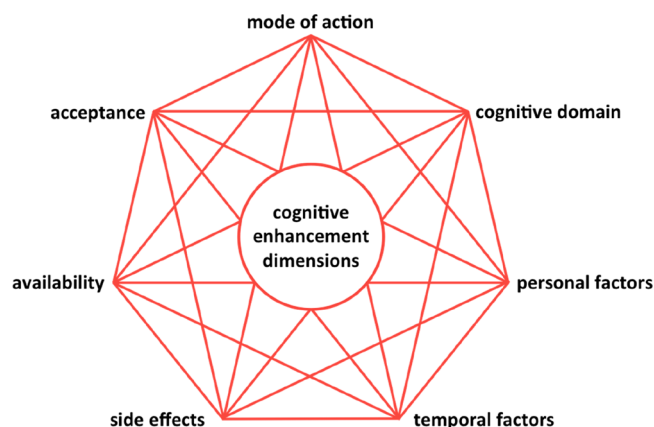


Figure 1. Cognitive enhancement interventions differ across several interdependent dimensions.

2. MODE OF ACTION

A widely cited definition characterizes enhancement as interventions in humans that aim to improve mental functioning beyond what is necessary to sustain or restore good health.¹ While the current bioethical debate on cognitive enhancement is strongly focused on pharmacological ways of enhancement, improving mental capabilities also by nonpharmacological means has to be considered as cognitive enhancement proper according to the given characterization. We have reviewed

elsewhere the efficacy of a number of nonpharmacological enhancers.^{2,3} To systematize the vast variety of different approaches of cognitive enhancement, we suggest clustering enhancement strategies into three major areas according to their main mode of action. Even though boundaries are not strict, most cognitive enhancement strategies can be considered to work as either biochemical, physical, or behavioral interventions (Figure 2). In the following, we will give an overview on the different cognitive enhancement strategies within these clusters.

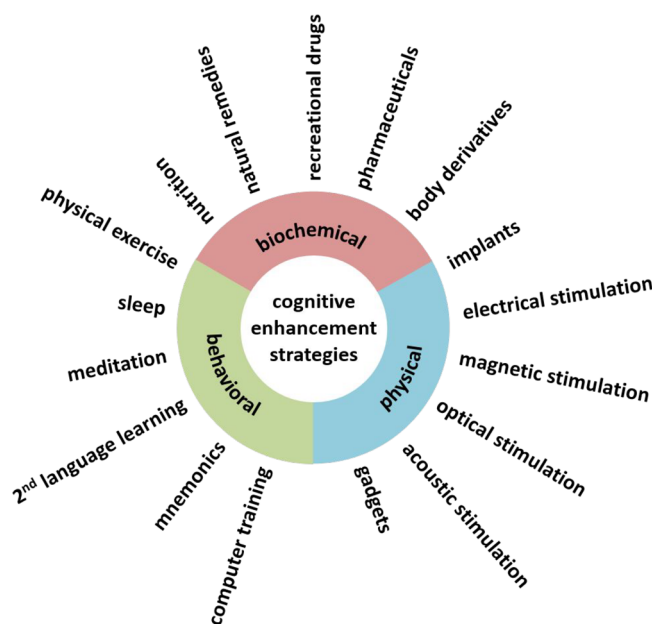


Figure 2. Cognitive enhancement interventions different in their mode of actions.

2.1. Biochemical Strategies. The prototypical cognitive enhancers addressed in the public debate are biochemical agents. However, biochemical interventions are not restricted to pharmaceutical “smart drugs”. Also application of ordinary substances such as oxygen has been shown to increase, e.g., memory processes^{4,5} and neural activation in memory-related brain regions.⁶

Biochemical enhancers with the longest tradition in human history are strategies to make use of certain nutritional components. Most widely used are probably glucose⁷ and caffeine,^{8,9} which both have demonstrated cognition-enhancing effects in numerous studies. In addition to coffee, other beverages from caffeine-bearing plants such as guarana have shown to enhance cognition.¹⁰ While the noncaffeine components in caffeine-bearing plants might exert independent effects on cognition,¹¹ it has been doubted that industrially designed drinks contain cognitive enhancing components that go beyond caffeine, glucose, or guarana extract.¹² Further nutritional components with some evidence for cognitive enhancing effects are flavonoids, e.g., in cocoa,^{13,14} curry powder (most likely due to the curcumin that it contains,^{15,16} folic acid,¹⁷ or omega-3 fatty acids.¹⁸ Besides specific dietary supplements, also the absence of food might enhance cognition: some evidence has been reported that fasting and general caloric restriction might improve memory in elderly individuals.^{19,20}

Also certain traditional natural remedies have been discussed as cognitive enhancers: besides herbs that also grow in Western regions such as salvia,²¹ particularly traditional Chinese and

Indian herbal medicines such as *Bacopa monnieri* have been ascribed with cognitive enhancing effects.^{22,23} However, with ginseng and ginkgo biloba, the most prominent examples of such traditional Asian herbal remedies so far have failed to consistently show positive effects on cognitive functions in healthy individuals.^{24,25}

A further biochemical intervention with a long history concerns drugs that are being used recreationally and that have demonstrated the potential to enhance certain cognitive functions. For example, nicotine improves attention and memory,^{26–28} and even alcohol, despite impairing many cognitive functions, might enhance others such as creative processes^{29,30} or, retroactively, memory.³¹

Pharmaceuticals are in particular by the public regarded as prototypical cognitive enhancers: synthetic stimulants such as amphetamine, methylphenidate, or modafinil, or antimentia drugs such as acetylcholinesterase inhibitors and memantine are at the core of public debate on cognitive enhancement. However, evidence for their efficacy for augmenting brain function and cognition in healthy subjects is often markedly lower than assumed in theoretical discussions.^{32–37} Importantly, the lack of an objective effect on cognition can be accompanied by a considerable placebo effect: for example, users who believed to have received mixed-amphetamine salts subjectively rated themselves as performing better and even show minor objective performance increases, independent of actual medication state.³⁸

While pharmacological enhancers are typically designed to affect or mimic certain neurotransmitters, also neural signaling molecules themselves such as adrenaline,³⁹ GABA,⁴⁰ glucocorticoids,⁴¹ ovarian hormones,⁴² and different neuropeptides^{43–45} have been suggested as cognitive enhancers.

A further biochemical strategy for cognitive enhancement consists of genetic modifications, which have been demonstrated to augment several learning and memory processes in animal models.^{46–51} Although progress has also been made in elucidating the genetic basis of cognitive traits in humans,⁵² genetic modifications in humans still have to be considered as future strategies rather than currently available enhancement options.

2.2. Physical Strategies. The current most widely discussed physical strategies for cognitive enhancement include a number of brain stimulation technologies. Whereas the cognition enhancing effects of invasive methods such as deep brain stimulation^{53,54} are restricted to subjects with pathological conditions, several forms of allegedly noninvasive stimulation strategies are increasingly used on healthy subjects, among them electrical stimulation methods such transcranial direct current stimulation (tDCS⁵⁵), transcranial alternating current stimulation (tACS⁵⁶), transcranial random noise stimulation (tRNS⁵⁷), transcranial pulsed current stimulation (tPCS^{58,59}), transcutaneous vagus nerve stimulation (tVNS⁶⁰), or median nerve stimulation (MNS⁶¹). Details of the stimulation procedures appear to be crucial: commercial do-it-yourself electrical brain stimulators might impair rather than enhance cognition,⁶² and systematic reviews have shed doubt on a clear and simple enhancing effect of electrical brain stimulation on different cognitive domains also under controlled laboratory conditions.^{63,64} Recent studies have even questioned if some of the most commonly used setups for electrical brain stimulation have neurophysiologically meaningful effects at all.^{65–68} On this background, the development of noninvasive deep brain stimulation via temporally interfering electric fields might

provide a more systematic and targeted mechanism compared to the currently used approaches.⁶⁸

Besides electrical stimulation methods, also for transcranial magnetic stimulation (TMS⁶⁹), optical stimulation with lasers,⁷⁰ and several forms of acoustic stimulation, such as transcranial focused ultrasound stimulation,⁷¹ binaural beats,^{72,73} or auditory stimulation of the EEG theta rhythm⁷⁴ or sleep EEG slow oscillations,⁷⁵ a potential for cognitive enhancement has been reported.

Physical enhancement methods that target brain processes more indirectly include whole body vibrations,⁷⁶ stochastic resonance motor control improvement,^{77,78} and several forms of neurofeedback,⁷⁹ with, e.g., EEG neurofeedback in the upper alpha band enhancing memory,⁸⁰ working memory,⁸¹ and visuospatial skills.⁸² Besides classical neurofeedback training that involves unspecific but active effort of the subject, also neurofeedback interventions that automatically feedback low energy currents in response to EEG activity have been developed, thereby allowing the subject to receive the training procedure passively.⁸³ Recently, the use of fMRI neurofeedback, utilizing multivariate pattern analysis, has shown the potential to increase sustained attention⁸⁴ or visuospatial memory.⁸⁵

Finally, humans have always deployed physical tools to assist cognitive functioning. In current developments that converge minds and machines, these tools become more closely integrated with the person.⁸⁶ Crowdfunding or biohacking communities have developed numerous novel technical devices to increase cognitive functions transiently with, e.g., wearable electronic memory aids or augmented reality gadgets,^{87,88} or more permanently as in the case of cognition enhancing or extending bodily implants.^{88,89} Neural implants or prosthetics have progressed; in controlled laboratory settings, implants could facilitate human memory.⁹⁰ In addition, Brain–Computer Interfaces connect the central nervous system with computers through wearable or implanted electrodes and may afford a range of applications that enhance cognitive functions or joint outputs of minds coupled with machines.^{91,92}

2.3. Behavioral Strategies. Although not commonly recognized as such by the public, cognitive enhancers with the most wide use and longest history are probably behavioral strategies: a rapidly growing body of evidence shows that everyday activities such as sleep⁹³ or physical exercise^{94–96} improve cognitive functioning. Also well-established cultural activities such as musical training,^{97,98} dancing,⁹⁹ or learning a second language¹⁰⁰ have been demonstrated to enhance cognition beyond the specifically trained skills.

In addition to these natural and cultural standard activities, several behavioral strategies have been developed to enhance certain brain functions intentionally. Two strategies that reach back to ancient times are mnemonic techniques to enhance learning and memory^{101,102} and meditation training to enhance attention processes and mindfulness.^{103,104} In contrast, commercial video games^{105,106} and customized computer trainings¹⁰⁷ represent historically very recent developments that are targeted to enhance specific cognitive capacities and skills. In contrast to several years of enthusiasm and widespread commercial application, however, more recent controlled studies and meta-analyses have shed some doubt on the efficacy of computerized brain training programs,¹⁰⁸ particularly criticizing claims of “far transfer” of training gains to cognitive domains considerably different from the specifically trained skills.^{109,110}

3. COGNITIVE DOMAIN

The human mind is not a monolithic entity, but consists of a broad variety of cognitive functions. Not surprisingly, no single cognitive enhancer augments every cognitive function. Instead, most cognitive enhancers have specific profiles regarding their efficacy for different cognitive domains. Memory is, e.g., strongly enhanced by mnemonic strategies, but not by meditation; attention, in turn, is strongly enhanced by meditation training, but not training in mnemonic strategies.^{101,103,104} Sleep, in contrast, enhances both cognitive capacities.^{111,112} Some computerized cognitive trainings have been found to enhance memory, processing speed and visuospatial skills, but not executive functions or attention.¹⁰⁷ It is currently highly debated in how far specific training strategies exert transfer effects also to nontrained cognitive domains.¹¹³

Different cognitive tasks require different optimal levels of receptor activation, thus requiring different doses of pharmacological enhancers targeting the respective neurotransmitter system depending on the cognitive domain targeted.¹¹⁴ Of note, effects of pharmacological enhancement on different cognitive domains might even differ depending on the cognitive test battery used, illustrating the fragility of the respective effects.¹¹⁵

Some interventions might even enhance one but impair another cognitive domain: Intranasal application of oxytocin has been shown to enhance social cognition and cognitive flexibility but impairs long-term memory.^{116,117} Methylphenidate improves the ability to resist distraction but impairs cognitive flexibility.¹¹⁸ Computerized working memory training has been reported to enhance working memory, reasoning, and arithmetic abilities; however, it might deteriorate creativity.¹¹⁹ Also for amphetamines and modafinil, potential impairments on creativity are discussed besides their enhancing effects on other domains.^{120,34} In contrast, alcohol might enhance creative processes while impairing most other cognitive functions.²⁹

The costs and benefits of a single cognitive enhancer might even change through slight changes in the application process: for example, electrical stimulation of posterior brain regions was found to facilitate numerical learning, whereas automaticity for the learned material was impaired. In contrast, stimulation on frontal brain regions impaired the learning process, whereas automaticity for the learned material was enhanced.¹²¹ Brain stimulation has thus been suggested to be a zero-sum game, with costs in some cognitive functions always being paid for gains in others.¹²² This implies that enhancement may have to be tuned to the task at hand, in order to focus on the currently most important cognitive demands.

4. PERSONAL FACTORS

The efficacy of cognitive enhancers does not only differ for different cognitive domains, but also for different users. An important factor in this regard are the cognitive skills of the individual prior to the enhancement intervention. Many pharmaceuticals, including amphetamine,¹²³ modafinil, and methylphenidate,¹²⁴ work mainly in individuals with low baseline performance. In some cases, even impairments in individuals with higher performance at baseline have been reported, e.g., in the case of amphetamine,¹²⁵ methylphenidate,¹²⁴ nicotine,²⁷ or acute choline supplementation.¹²⁶ The phenomenon of enhanced cognition in individuals with low baseline performance and impairments in those with high baseline performance can be explained by the classical inverted U-model,^{127,128} where performance is optimal at intermediate

levels of the targeted neurochemicals and impaired at levels that are either too low or too high.^{129–131} For some drugs such as methylphenidate, enhancement dependency on the baseline might even differ between cognitive functions, with performance in specific tasks being improved in low, while impaired in high, performers,¹²⁴ but showing the opposite pattern for other tasks.¹³²

The baseline-dependency of cognitive enhancement is not restricted to pharmaceuticals: also in the case of video games,¹³³ cognitive training,¹³⁴ or brain stimulation,^{135,136} individuals starting at a lower baseline performance benefit more than those with an already high performance at baseline. In contrast, sleep appears to improve memory particularly in subjects with a higher baseline performance of memory,¹³⁷ working memory¹³⁸ or intelligence.¹³⁹ Also mnemonic training appears to work particularly well in individuals with a higher cognitive baseline performance.¹⁴⁰ This has been interpreted in terms of an amplification model, in which high baseline performance and cognitive enhancement interventions show synergistic effects.¹⁴¹

Cognitive enhancers can also affect individuals differently depending on basic biological, psychological, or social factors. For example, effects of training interventions on selective attention can depend on the genotype of the trainee;¹⁴² effects of methylphenidate on creativity can depend on personality characteristics;¹⁴³ the cognition enhancing effects of sleep¹⁴⁴ or video games¹⁴⁵ are modulated by gender. In turn, such modulations of enhancement effects might reduce existing differences in cognitive profiles, as seen, e.g., in action video game training, that have the potential to eliminate gender differences in spatial attention and decrease the gender disparity in mental rotation ability.¹⁴⁶ Also the hormonal status of subjects affects how strongly they profit, e.g., from sleep^{144–148} or brain stimulation.¹⁴⁹ Caffeine enhances working memory particularly in extraverted individuals,¹⁵⁰ and memory enhancement through sleep¹⁵¹ or mnemonic training¹⁴⁰ has been reported to depend on the age of subjects. Health status affects how much users benefit from different kinds of cognitive enhancers, including pharmaceuticals,³ mnemonics,¹⁵² or sleep.^{153–156} Finally, also socioenvironmental factors such as social resources, parental occupation, or family composition can modulate cognitive enhancement interventions, e.g., with cognitive training programs.¹⁵⁷

5. TIME SCALE

Interventions for cognitive enhancement differ in the specific time scale they require to achieve their aims. The prototypical “smart pill” discussed in popular accounts of cognitive enhancement needs practically no preparation time, exerts its effects within seconds or minutes, and lasts for several hours. While this is close to reality in the case of some pharmacological enhancers, the temporal pattern of most other enhancement strategies differs strongly from these time scales. In particular, the time needed for application and the duration of their effects markedly varies between enhancement interventions.

Most pharmacological enhancers can be applied quickly and without further preparation; however, some drugs such as acetylcholinesterase inhibitors or memantine are thought to require longer periods of intake to be effective.³³ Also some nutritional enhancers such as glucose and caffeine exert their effects rather quickly, whereas other nutritional supplements have to be taken over extended periods to show an impact on cognition.^{158,18} Obviously, behavioral strategies like sleep,

exercise, video games or mnemonic training need hours or weeks to robustly enhance cognition. Some effects of meditation might even take years of training.¹⁵⁹ For brain stimulation methods, both immediate effects of acute stimulation, but also more delayed effects after repeated stimulation have been observed.^{55,69} Technological gadgets or implants need some preparation to be installed and accommodated to, however then exert their cognition augmenting effects on demand.

Enhancing effects of most quickly acting pharmacological or nutritional cognitive enhancers also wear off rather rapidly. In contrast to such transient effects, interventions such as brain stimulation,^{160,161,57} sleep,¹⁶² mnemonic strategies¹⁶³ or genetic modifications⁴⁶ have the potential for long-term up to chronic enhancement. However, in the latter case, the reversibility of the effects (and side effects) of an enhancement intervention might be a further aspect to be considered.

Interventions can also differ regarding the time point of application relative to the situation when enhanced cognitive performance is needed. For example, application of stress hormones such as cortisol or adrenaline before or after memory encoding enhances memory, whereas application before retrieval impairs memory;⁴¹ benzodiazepines impair memory when given before and enhance memory when given after encoding;¹⁶⁴ in contrast, caffeine before learning enhances memory under certain conditions but might impair memory when consumed afterward.^{165,9} Mnemonic strategies on the other hand work solely when taught/applied before/during encoding, but can hardly be applied afterward.

Finally, some interventions can also influence the timing of cognitive performance itself: stimulants such as methylphenidate, modafinil, and caffeine might increase the time subjects take to perform a given task, with impairing effects under time pressure and potentially enhancing effects in the absence of temporal constraints.¹⁶⁶

6. SIDE EFFECTS

The pharmaceutical platitude that there is no effect without side effects holds true also for many nonpharmacological enhancement interventions. It appears obvious that cognitive enhancers differ in the severity and form of side effects: *prima facie*, deep brain stimulation or implants have higher risks for side effects than sleep or cognitive training. However, also more indirect enhancement strategies such as neurofeedback potentially bear the risk of side effects up to inducing epileptiform activity,¹⁶⁷ and even gentle intervention such as meditation training might exert negative effects on specific cognitive domains: a negative relationship between mindfulness and implicit learning^{168,169} and an increased susceptibility to false memory formation after mindfulness meditation¹⁷⁰ have been observed. Here, the intended training goal of nonjudgemental mindfulness opposes tasks where either a more critical or automatic mindset was needed. Further examples of side effects intrinsically associated with the enhancement goal are trade-offs between stability vs flexible updating of memory systems:¹²⁹ memories can also become “too stable” due to a memory enhancement intervention, as observed, e.g., for the anti-obesity drug rimonabant.¹⁷¹

It has been suggested to differentiate enhancement strategies according to their level of invasiveness.^{172,173} However, while invasiveness has a more or less definite meaning in its original medical context, physically breaching the skin or entering the body deeply through an external orifice,¹⁷⁴ it is difficult to determine the level of invasiveness in the context of cognitive

enhancement. Both nutritional supplements and pharmaceuticals enter the body, and thus could be considered invasive in a narrow medical sense, as might be certain forms of physical exercise due to the risk of bruises or scratches as common, e.g., in martial arts or a hike through the woods. Brain stimulation that does not break the skin would, by contrast, be classified as noninvasive. This taxonomy can be disputed for good reasons.¹⁷⁵ Besides known risks of these stimulation methods such as scalp burns from tDCS or seizures from TMS, the “known unknowns” have been suggested to pose potentially even greater risks: potential build-up effects across multiple sessions or in sensitive nontarget areas.¹⁷⁶ Of note, only few neuroscientists use brain stimulation on themselves for cognitive enhancement.¹⁷⁶ Given the still unclear risks and side effects of do-it-yourself brain stimulation use, it has been proposed to extend existing medical device legislation to cover also nonpharmacological and in particular physically acting cognitive enhancement devices.^{177,178} In contrast to strict medical definitions, the more intuitively assessed level of invasiveness of an intervention often seems to depend on familiarity and cultural traditions. This leads to the Western attitude according to which changing one’s diet or performing exercise appears less invasive than taking pharmaceuticals or applying brain stimulation, independent of their actual effects on health.

Related to the time scale dimension, side effects of short- vs long-term use of cognitive enhancers can be differentiated. For example, while side effects for the acute use of methylphenidate include increased heart rate, headache, anxiety, nervousness, dizziness, drowsiness, and insomnia, in the case of long-term use side effects such as abnormal prefrontal brain function and impaired plasticity have been reported.^{179,180} Also addiction is a well-known side effect for the long-term use of pharmacological enhancers, which is particularly detrimental to the aim of enhancement if combined with tolerance effects such that larger doses are needed to achieve the same effect (or prevent impairing withdrawal effects). Also behavioral addictions have been observed, e.g., physical exercise¹⁸¹ or the use of technological gadgets.¹⁸²

A somewhat nonobvious negative effect of some cognitive enhancers is their illusionary efficacy: users sometimes believe their performance to be enhanced by amphetamine in absence of any verified and objectively visible enhancing effects, even if administered in a double blind manner.^{183,184,38} This is particularly counterproductive in cases of already high-functioning individuals whose cognitive capabilities might be impaired rather than enhanced by amphetamine.^{125,184} Also for caffeine, under certain conditions higher subjectively perceived mental energy in the absence of objectively enhancing effects have been observed.¹⁸⁵ The often subtle effects of enhancers can be hidden or amplified by placebo effects.

7. AVAILABILITY

Cognitive enhancers differ in at least three aspects of availability: legal status, cost, and application time. In terms of legal regulation, different enhancement methods are regulated by sometimes drastically varying frameworks. Pharmaceuticals, for instance, are regulated by strict international control regimes that effectively prohibit nontherapeutic uses or by more lenient domestic drug laws. Brain-stimulation methods, by contrast, fall under medical device regulations, pertaining to basic safety standards in terms but not proscribing the uses to which they might be put.^{177,178} Behavioral strategies are usually not regulated at all. The regulatory landscape is thus vast and

possibly incoherent (for a review, see ref 186). Besides practical hurdles to the acquisition of illicit drugs for cognitive enhancement, the legal status appears to affect the motivation of users to decide which cognitive enhancers to take.¹⁶⁶

A common ethical argument in the enhancement debate concerns distributive justice: also legally available enhancers come with cost barriers, restricting individuals of low socioeconomic status from access.¹⁸⁷ A main factor in the costs of cognitive enhancers is their patentability, which is not restricted to pharmaceuticals.¹⁸⁸ However, in particular, behavioral enhancement strategies are typically not subject to patentability or other cost-driving factors: sleep, exercise, meditation, or training in mnemonic strategies are largely free of cost and, thus, in contrast to pharmaceuticals or technological strategies, are available independent from the financial background of the user. On the other hand, these behavioral strategies require some time and effort: the 24/7 working manager as the cliché user of cognitive enhancement drugs might have the financial means to afford quickly taking his expensive smart pill between two meetings, but might be unable or unwilling to spend extended periods of time with sleep, meditation, or mnemonic training.

8. SOCIAL ACCEPTANCE

Largely independent from their specific enhancing effects on different cognitive capacities, social acceptance of cognitive enhancement interventions differs strongly depending on traditions, their perceived naturalness, and the perceived directness of their mode of action. Enhancement interventions with a tradition of thousands of years such as meditation and nutrition are typically much better accepted than many currently debated enhancement strategies such as brain stimulation and pharmaceuticals.¹⁸⁹ Also more “natural” interventions such as sleep or exercise are seen in a more positive light compared to technological innovations.¹⁹⁰ Moreover, in how far the mode of action is perceived as psychologically mediated or more biologically direct, affecting the brain indirectly through the senses or more directly through the cranium or metabolism, often plays a role for their social acceptance: if an enhancement intervention such as intense cognitive or physical training requires extended efforts or is seen as a quick and effortless shortcut to the same goal as in the case of smart pills or brain stimulation touches different intuitions about human virtues and is thus valued differently. Even though views based on such purely intuitive aspects of tradition, naturalness, or directness often rely on cognitive biases rather than rational argument,¹⁹¹ a negative social perception for whatever reason might generate indirect psychological costs for users, which in turn might influence also rational evaluations of the respective enhancement intervention.¹⁹²

Accordingly, one of the central points in the ethical controversy revolves around the question of whether enhancement strategies only relevantly differ with respect to their outcomes, i.e., their benefits and side effects,¹⁹³ or also with respect to their mode of operation.¹⁹⁴ Some argue that the relevant ethical distinction runs along the lines of enhancements that are active, in the sense of requiring participation, and those that work on persons more passively.¹⁹⁵

Not surprisingly, different views on cognitive enhancement prevail in different (sub)cultures, with, e.g., a more positive view on enhancement interventions in Asia¹⁹⁶ or in younger populations.¹⁹⁷ Empirical studies on attitudes toward cognitive enhancement interventions found medical safety, coercion, and fairness the most common concerns, with nonusers displaying

more concerns regarding medical safety and fairness than users.¹⁹⁸ Sometimes readily available substances for cognitive enhancement such as caffeine, energy drinks, or herbal drugs are dubbed “soft enhancers”;¹⁹⁹ however, considering that prohibition of substances is not only based on their potential harm, but also on historical circumstances, this differentiation between soft and hard enhancers appears questionable.

A further aspect that determines the social acceptance of cognitive enhancement is the aim of the given intervention. Taken by face value, the term *cognitive enhancement* denotes any action or intervention that improves cognitive capacities, independent from the specific aim of this improvement. The use of the term in the empirical, philosophical, and sociopolitical literature, however, varies with regard to the specific aim of enhancement interventions: people appear to be more tolerant toward enhancement of traits considered less fundamental to self-identity,²⁰⁰ and also more tolerant toward enhancement in individuals with cognitive impairments or low performance baselines compared to enhancement of normal or high achievers.^{201,202} At least four different aims can be identified, each leading to different research strategies and different ethical evaluations of existing or potential enhancement strategies.²⁰³ The least problematic concept of cognitive enhancement targets those everyday medical or psychological interventions that are meant to treat pathological deficiencies. Closely related are those cognitive enhancement interventions that aim to prevent or attenuate cognitive decline that is associated also with healthy aging.²⁰⁴ Slightly less accepted appear to be those enhancement strategies that aim to improve cognition in completely healthy individuals, but still clearly stay within the normal limits of cognition. The probably most widely used and ethically most controversial concept of cognitive enhancement aims at the augmentation of cognitive capacities beyond normal function, as is represented in the cliché of high-functioning students or managers trying to further improve their performance by taking smart pills.

Besides these differentiations between enhancement of impaired vs healthy cognition, another difference in the aims of cognitive enhancement touches the ultimate deed of the enhancement intervention: due to the central role of cognitive capacities in defining humans as a species, it is tempting to consider the improvement of these defining human capacities as a value in itself. However, most philosophical or religious approaches do not center on objective cognitive performance markers, but propose values only indirectly related to cognitive performance such as living a happier or more meaningful life in general. In this light, human enhancement in more general terms does not need to aim for individual cognitive or neural processes, but can also be achieved by sociopolitical reforms targeted at the population level.^{205,206}

9. CONCLUSIONS

Cognitive enhancement clearly is a multidimensional endeavor. However, not every dimension is important for every theoretical or empirical research question. For example, many empirical researchers of cognitive enhancement are primarily interested in the understanding of the neurobiological and psychological mechanisms underlying cognitive functions.²⁰⁷ For this aim, the availability and social acceptance dimensions are largely irrelevant. In contrast, many theorists are interested in the social and ethical implications of cognitive enhancement,²⁰⁸ where these dimensions might be of prime importance. Also side effects and temporal factors might be of secondary importance

to empirical researchers with an interest in the neural mechanisms of certain cognitive processes, whereas these would be highly relevant for users who ponder the question which cognitive enhancement strategy to choose for a certain aim. When comparing different cognitive enhancement strategies, different dimensions might thus be differently weighed or completely ignored, depending on the aim of the comparison.

Up until now, direct comparisons between cognitive enhancement strategies with radically different modes of actions have rarely been made (but see, e.g., ref 165), and more comprehensive comparisons across dimensions might be difficult: practical issues of information availability from the different dimensions aside, interventions typically differ on different dimensions and are thus difficult to compare globally. In addition, multiple interactions between different enhancers exist, which further complicates the situation. Interactions have been reported, e.g., for glucose and caffeine,²⁰⁹ diet and exercise,²¹⁰ exercise and working memory training,²¹¹ video games and sleep,²¹² video games and brain stimulation,²¹³ exercise and brain stimulation,²¹⁴ and brain stimulation and sleep.^{215,216} Also different dimensions discussed here can interact in multiple ways, as, e.g., computerized cognitive training can differentially enhance different cognitive processes depending on personal factors such as age;²¹⁷ and social acceptance of different enhancement strategies depends on both the baseline performance of users and the cognitive domain targeted.^{200,201}

Despite—or because of—these complexities, in our opinion, both theoretical discussions and empirical research would strongly benefit from a more differentiated approach. Specific research questions might require the emphasis on some dimensions of cognitive enhancement over others, and for some research questions some dimensions might be entirely irrelevant. Nevertheless, keeping in mind that cognitive enhancement is not a monolithic phenomenon will help to solve and avoid a number of confusions and disagreements that are still present in the public debate on cognitive enhancement.

AUTHOR INFORMATION

Corresponding Author

*Mailing address: Donders Institute for Brain, Cognition and Behaviour, Kapittelweg 29, 6525 EN Nijmegen, The Netherlands. Tel. ++31-24-3610984.

ORCID

Martin Dresler: 0000-0001-7441-3818

Author Contributions

All authors developed the concept of this paper and jointly wrote the manuscript.

Funding

This work was supported by the Volkswagen Foundation, Germany.

Notes

The authors declare no competing financial interest.

REFERENCES

- (1) Juengst, E. T. (1998) What does enhancement mean? In *Enhancing Human Traits: Ethical and Social Implications* (Parens, E., Ed.), pp 29–47, Georgetown University Press.
- (2) Dresler, M., Sandberg, A., Ohla, K., Bubltz, C., Trenado, C., Mroczko-Wąsowicz, A., Kühn, S., and Repantis, D. (2013) Non-

pharmacological cognitive enhancement. *Neuropharmacology* 64, 529–43.

(3) Dresler, M., and Repantis, D. (2015) Cognitive enhancement in humans. In *Cognitive Enhancement: Pharmacologic, Environmental and Genetic Factors* (Knafo, S., and Venero, C., Eds.), pp 273–306, Elsevier, Amsterdam.

(4) Moss, M. C., and Scholey, A. B. (1996) Oxygen administration enhances memory formation in healthy young adults. *Psychopharmacology (Berl)* 124, 255–60.

(5) Scholey, A. B., Moss, M. C., Neave, N., and Wesnes, K. (1999) Cognitive performance, hyperoxia, and heart rate following oxygen administration in healthy young adults. *Physiol. Behav.* 67, 783–9.

(6) Yu, R., Wang, B., Li, S., Wang, J., Zhou, F., Chu, S., He, X., Wen, X., Ni, X., Liu, L., Xie, O., and Huang, R. (2015) Cognitive enhancement of healthy young adults with hyperbaric oxygen: A preliminary resting-state fMRI study. *Clin. Neurophysiol.* 126, 2058–2067.

(7) Smith, M. A., Riby, L. M., Eekelen, J. A., and Foster, J. K. (2011) Glucose enhancement of human memory: a comprehensive research review of the glucose memory facilitation effect. *Neurosci. Biobehav. Rev.* 35, 770–83.

(8) Glade, M. J. (2010) Caffeine-Not just a stimulant. *Nutrition* 26, 932–8.

(9) Nehlig, A. (2010) Is caffeine a cognitive enhancer? *J. Alzheimer's Dis.* 20, S85–94.

(10) Haskell, C. F., Kennedy, D. O., Wesnes, K. A., Milne, A. L., and Scholey, A. B. (2007) A double-blind, placebo-controlled, multi-dose evaluation of the acute behavioural effects of guaraná in humans. *J. Psychopharmacol.* 21, 65–70.

(11) Haskell, C. F., Dodd, F. L., Wightman, E. L., and Kennedy, D. O. (2013) Behavioural effects of compounds co-consumed in dietary forms of caffeinated plants. *Nutr. Res. Rev.* 26, 49–70.

(12) McLellan, T. M., and Lieberman, H. R. (2012) Do energy drinks contain active components other than caffeine? *Nutr. Rev.* 70, 730–44.

(13) Rendeiro, C., Guerreiro, J. D., Williams, C. M., and Spencer, J. P. (2012) Flavonoids as modulators of memory and learning: molecular interactions resulting in behavioural effects. *Proc. Nutr. Soc.* 71, 246–62.

(14) Socci, V., Tempesta, D., Desideri, G., De Gennaro, L., and Ferrara, M. (2017) Enhancing Human Cognition with Cocoa Flavonoids. *Frontiers in Nutrition* 4, 19.

(15) Ng, T. P., Chiam, P. C., Lee, T., Chua, H. C., Lim, L., and Kua, E. H. (2006) Curry consumption and cognitive function in the elderly. *Am. J. Epidemiol.* 164, 898–906.

(16) Cox, K. H., Pipingas, A., and Scholey, A. B. (2015) Investigation of the effects of solid lipid curcumin on cognition and mood in a healthy older population. *J. Psychopharmacol.* 29, 642–51.

(17) Enderami, A., Zarghami, M., and Darvishi-Khezri, H. (2018) The effects and potential mechanisms of folic acid on cognitive function: a comprehensive review. *Neurol. Sci.* 39, 1667.

(18) Luchtman, D. W., and Song, C. (2013) Cognitive enhancement by omega-3 fatty acids from child-hood to old age: findings from animal and clinical studies. *Neuropharmacology* 64, 550–565.

(19) Witte, A. V., Fobker, M., Gellner, R., Knecht, S., and Flöel, A. (2009) Caloric restriction improves memory in elderly humans. *Proc. Natl. Acad. Sci. U. S. A.* 106, 1255–60.

(20) Brandhorst, S., Choi, I. Y., Wei, M., Cheng, C. W., Sedrakyan, S., Navarrete, G., Dubeau, L., Yap, L. P., Park, R., Vinciguerra, M., Di Biase, S., Mirzaei, H., Mirisola, M. G., Childress, P., Ji, L., Groshen, S., Penna, F., Odetti, P., Perin, L., Conti, P. S., Ikeno, Y., Kennedy, B. K., Cohen, P., Morgan, T. E., Dorff, T. B., and Longo, V. D. (2015) A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan. *Cell Metab.* 22, 86–99.

(21) Tildesley, N. T., Kennedy, D. O., Perry, E. K., Ballard, C. G., Savelev, S., Wesnes, K. A., and Scholey, A. B. (2003) Salvia lavandulaefolia (Spanish sage) enhances memory in healthy young volunteers. *Pharmacol., Biochem. Behav.* 75, 669–74.

(22) Howes, M. J., and Houghton, P. J. (2003) Plants used in Chinese and Indian traditional medicine for improvement of memory and cognitive function. *Pharmacol., Biochem. Behav.* 75, 513–27.

- (23) Kongkeaw, C., Dilokthornsakul, P., Thanarangsarit, P., Limpeanchob, N., and Norman Scholfield, C. (2014) Meta-analysis of randomized controlled trials on cognitive effects of *Bacopa monnieri* extract. *J. Ethnopharmacol.* 151, 528–35.
- (24) Geng, J., Dong, J., Ni, H., Lee, M. S., Wu, T., Jiang, K., Wang, G., Zhou, A. L., and Malouf, R. (2010) Ginseng for cognition. *Cochrane Database Syst. Rev.* 12, CD007769.
- (25) Laws, K. R., Sweetnam, H., and Kondel, T. K. (2012) Is Ginkgo biloba a cognitive enhancer in healthy individuals? A meta-analysis. *Hum. Psychopharmacol.* 27, 527–33.
- (26) Warburton, D. M. (1992) Nicotine as a cognitive enhancer. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 16, 181–91.
- (27) Niemegeers, P., Dumont, G., Quisenbaerts, C., Morrens, M., Boonzaier, J., Fransen, E., de Bruijn, E., Hulstijn, W., and Sabbe, B. (2014) The effects of nicotine on cognition are dependent on baseline performance. *Eur. Neuropsychopharmacol.* 24, 1015–1023.
- (28) Valentine, G., and Sofuoglu, M. (2018) Cognitive Effects of Nicotine: Recent Progress. *Curr. Neuropharmacol.* 16, 403–414.
- (29) Jarosz, A. F., Colflesh, G. J., and Wiley, J. (2012) Uncorking the muse: alcohol intoxication facilitates creative problem solving. *Conscious Cogn* 21, 487–93.
- (30) Benedek, M., Panzner, L., Jauk, E., and Neubauer, A. C. (2017) Creativity on tap? Effects of alcohol intoxication on creative cognition. *Conscious Cogn* 56, 128–134.
- (31) Carlyle, M., Dumay, N., Roberts, K., McAndrew, A., Stevens, T., Lawn, W., and Morgan, C. J. A. (2017) Improved memory for information learnt before alcohol use in social drinkers tested in a naturalistic setting. *Sci. Rep.* 7, 6213.
- (32) Repantis, D., Schlattmann, P., Laisney, O., and Heuser, I. (2010) Modafinil and methylphenidate for neuroenhancement in healthy individuals: A systematic review. *Pharmacol. Res.* 62, 187–206.
- (33) Repantis, D., Laisney, O., and Heuser, I. (2010) Acetylcholinesterase inhibitors and memantine for neuroenhancement in healthy individuals: a systematic review. *Pharmacol. Res.* 61, 473–81.
- (34) Battleday, R. M., and Brem, A. K. (2015) Modafinil for cognitive neuroenhancement in healthy non-sleep-deprived subjects: A systematic review. *Eur. Neuropsychopharmacol.* 25, 1865–81.
- (35) Fond, G., Micoulaud-Franchi, J. A., Brunel, L., Macgregor, A., Miot, S., Lopez, R., et al. (2015) Innovative mechanisms of action for pharmaceutical cognitive enhancement: a systematic review. *Psychiatry Res.* 229, 12–20.
- (36) Murillo-Rodríguez, E., Barciela Veras, A., Barbosa Rocha, N., Budde, H., and Machado, S. (2018) An Overview of the Clinical Uses, Pharmacology, and Safety of Modafinil. *ACS Chem. Neurosci.* 9, 151–158.
- (37) Schleim, S., and Quednow, B. B. (2018) How Realistic Are the Scientific Assumptions of the Neuroenhancement Debate? Assessing the Pharmacological Optimism and Neuroenhancement Prevalence Hypotheses. *Front. Pharmacol.* 9, 3.
- (38) Cropsey, K. L., Schiavon, S., Hendricks, P. S., Froelich, M., Lentowicz, I., and Fargason, R. (2017) Mixed-amphetamine salts expectancies among college students: Is stimulant induced cognitive enhancement a placebo effect? *Drug Alcohol Depend.* 178, 302–309.
- (39) Cahill, L., and Alkire, M. T. (2003) Epinephrine enhancement of human memory consolidation: interaction with arousal at encoding. *Neurobiol. Learn. Mem.* 79, 194–8.
- (40) Steenbergen, L., Sellaro, R., Stock, A. K., Beste, C., and Colzato, L. S. (2015) γ -Aminobutyric acid (GABA) administration improves action selection processes: a randomised controlled trial. *Sci. Rep.* 5, 12770.
- (41) Het, S., Ramlow, G., and Wolf, O. T. (2005) A meta-analytic review of the effects of acute cortisol administration on human memory. *Psychoneuroendocrinology* 30, 771–84.
- (42) Smith, M. J., Adams, L. F., Schmidt, P. J., Rubinow, D. R., and Wassermann, E. M. (2002) Effects of ovarian hormones on human cortical excitability. *Ann. Neurol.* 51, 599–603.
- (43) Kunath, N., and Dresler, M. (2014) Ghrelin and memory. In *Central Functions of the Ghrelin Receptor* (Portelli, J., and Smolders, I., Eds.), pp 167–176, Springer, New York.
- (44) Kunath, N., Müller, N., Tonon, M., Konrad, B. N., Kopczak, A., Pawlowski, M., Kühn, S., Repantis, D., Ohla, K., Müller, D., Fernandez, G., Tschoep, M., Steiger, A., Czigic, M., and Dresler, M. (2016) Ghrelin modulates encoding-related brain activity without enhancing memory formation in humans. *NeuroImage* 142, 465–473.
- (45) Asua, D., Bougama, G., Calleja-Felipe, M., Morales, M., and Knafo, S. (2018) Peptides acting as cognitive enhancers. *Neuroscience* 370, 81–87.
- (46) Tang, Y. P., Shimizu, E., Dube, G. R., Rampon, C., Kerchner, G. A., Zhuo, M., Liu, G., and Tsien, J. Z. (1999) Genetic enhancement of learning and memory in mice. *Nature* 401, 63–9.
- (47) Diana, G., Valentini, G., Travagione, S., Falzano, L., Pieri, M., Zona, C., Meschini, S., Fabbri, A., and Fiorentini, C. (2007) Enhancement of learning and memory after activation of cerebral Rho GTPases. *Proc. Natl. Acad. Sci. U. S. A.* 104, 636–641.
- (48) de Viti, S., Martino, A., Musilli, M., Fiorentini, C., and Diana, G. (2010) The Rho GTPase activating CNF1 improves associative working memory for object-in-place. *Behav. Brain Res.* 212, 78–83.
- (49) Dubal, D. B., Yokoyama, J. S., Zhu, L., Broestl, L., Worden, K., Wang, D., Sturm, V. E., Kim, D., Klein, E., Yu, G. Q., Ho, K., Eilertson, K. E., Yu, L., Kuro-o, M., De Jager, P. L., Coppola, G., Small, G. W., Bennett, D. A., Kramer, J. H., Abraham, C. R., Miller, B. L., and Mucke, L. (2014) Life extension factor klotho enhances cognition. *Cell Rep.* 7, 1065–1076.
- (50) Ounallah-Saad, H., Sharma, V., Edry, E., and Rosenblum, K. (2014) Genetic or pharmacological reduction of PERK enhances cortical-dependent taste learning. *J. Neurosci.* 34, 14624–32.
- (51) Martínez, G., Vidal, R. L., Mardones, P., Serrano, F. G., Ardiles, A. O., Wirth, C., Valdés, P., Thielen, P., Schneider, B. L., Kerr, B., Valdés, J. L., Palacios, A. G., Inestrosa, N. C., Glimcher, L. H., and Hetz, C. (2016) Regulation of Memory Formation by the Transcription Factor XBP1. *Cell Rep.* 14, 1382–1394.
- (52) Papassotiropoulos, A., and de Quervain, D. J. (2011) Genetics of human episodic memory: dealing with complexity. *Trends Cognit. Sci.* 15, 381–7.
- (53) Suthana, N., Haneef, Z., Stern, J., Mukamel, R., Behnke, E., Knowlton, B., and Fried, I. (2012) Memory enhancement and deep-brain stimulation of the entorhinal area. *N. Engl. J. Med.* 366, 502–10.
- (54) Inman, C. S., Manns, J. R., Bijanki, K. R., Bass, D. I., Hamann, S., Drane, D. L., Fasano, R. E., Kovach, C. K., Gross, R. E., and Willie, J. T. (2018) Direct electrical stimulation of the amygdala enhances declarative memory in humans. *Proc. Natl. Acad. Sci. U. S. A.* 115, 98–103.
- (55) Coffman, B. A., Clark, V. P., and Parasuraman, R. (2014) Battery powered thought: enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. *NeuroImage* 85, 895–908.
- (56) Santarnecchi, E., Polizzotto, N. R., Godone, M., Giovannelli, F., Feurra, M., Matzen, L., Rossi, A., and Rossi, S. (2013) Frequency-dependent enhancement of fluid intelligence induced by transcranial oscillatory potentials. *Curr. Biol.* 23, 1449–53.
- (57) Snowball, A., Tachtsidis, I., Popescu, T., Thompson, J., Delazer, M., Zamarian, L., et al. (2013) Long-term enhancement of brain function and cognition using cognitive training and brain stimulation. *Curr. Biol.* 23, 987–992.
- (58) Jaberzadeh, S., Bastani, A., and Zoghi, M. (2014) Anodal transcranial pulsed current stimulation: A novel technique to enhance corticospinal excitability. *Clin. Neurophysiol.* 125, 344–351.
- (59) Morales-Quezada, L., Cosmo, C., Carvalho, S., Leite, J., Castillo-Saavedra, L., Rozisky, J. R., and Fregni, F. (2015) Cognitive effects and autonomic responses to transcranial pulsed current stimulation. *Exp. Brain Res.* 233, 701.
- (60) Colzato, L. S., Ritter, S. M., and Steenbergen, L. (2018) Transcutaneous vagus nerve stimulation (tVNS) enhances divergent thinking. *Neuropsychologia* 111, 72–76.
- (61) Carvalho, S., French, M., Thibaut, A., Lima, W., Simis, M., Leite, J., and Fregni, F. (2018) Median nerve stimulation induced motor learning in healthy adults: A study of timing of stimulation and type of learning. *Eur. J. Neurosci.* 48, 1667.

- (62) Steenbergen, L., Sellaro, R., Hommel, B., Lindenberger, U., Kühn, S., and Colzato, L. S. (2016) "Unfocus" on focus: commercial tDCS headset impairs working memory. *Exp. Brain Res.* 234, 637–43.
- (63) Buch, E. R., Santarnecchi, E., Antal, A., Born, J., Celnik, P. A., Classen, J., Gerloff, C., Hallett, M., Hummel, F. C., Nitsche, M. A., Pascual-Leone, A., Paulus, W. J., Reis, J., Robertson, E. M., Rothwell, J. C., Sandrini, M., Schambra, H. M., Wassermann, E. M., Ziemann, U., and Cohen, L. G. (2017) Effects of tDCS on motor learning and memory formation: A consensus and critical position paper. *Clin. Neurophysiol.* 128, 589–603.
- (64) Reteig, L. C., Talsma, L. J., van Schouwenburg, M. R., and Slagter, H. A. (2017) Transcranial electrical stimulation as a tool to enhance attention. *J. Cogn. Enhanc.* 1, 10–25.
- (65) Lafon, B., Henin, S., Huang, Y., Friedman, D., Melloni, L., Thesen, T., Doyle, W., Buzsáki, G., Devinsky, O., Parra, L. C., and Liu, A. A. (2017) Low frequency transcranial electrical stimulation does not entrain sleep rhythms measured by human intracranial recordings. *Nat. Commun.* 8, 1199.
- (66) Thibaut, A., Zafonte, R., Morse, L. R., and Fregni, F. (2017) Understanding Negative Results in tDCS Research: The Importance of Neural Targeting and Cortical Engagement. *Front. Neurosci.* 11, 00707.
- (67) Parkin, B. L., Bhandari, M., Glen, J. C., and Walsh, V. (2018) The physiological effects of transcranial electrical stimulation do not apply to parameters commonly used in studies of cognitive neuromodulation. *Neuropsychologia*, DOI: 10.1016/j.neuropsychologia.2018.03.030.
- (68) Grossman, N., Bono, D., Dedic, N., Kodandaramaiah, S. B., Rudenko, A., Suk, H. J., Cassara, A. M., Neufeld, E., Kuster, N., Tsai, L. H., Pascual-Leone, A., and Boyden, E. S. (2017) Noninvasive Deep Brain Stimulation via Temporally Interfering Electric Fields. *Cell* 169, 1029.
- (69) Luber, B., and Lisanby, S. H. (2014) Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS). *NeuroImage* 85, 961–70.
- (70) Gonzalez-Lima, F., and Barrett, D. W. (2014) Augmentation of cognitive brain functions with transcranial lasers. *Front. Syst. Neurosci.* 8, 36.
- (71) Legon, W., Sato, T. F., Opitz, A., Mueller, J., Barbour, A., Williams, A., and Tyler, W. J. (2014) Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans. *Nat. Neurosci.* 17, 322–9.
- (72) Reedijk, S. A., Bolders, A., and Hommel, B. (2013) The impact of binaural beats on creativity. *Front. Hum. Neurosci.* 7, 786.
- (73) Colzato, L. S., Barone, H., Sellaro, R., and Hommel, B. (2017) More attentional focusing through binaural beats: evidence from the global-local task. *Hematol. Cell Ther.* 81, 271–277.
- (74) Roberts, B. M., Clarke, A., Addante, R. J., and Ranganath, C. (2018) Entrainment enhances theta oscillations and improves episodic memory. *Cogn. Neurosci.* 9, 181.
- (75) Ngo, H. V., Martinetz, T., Born, J., and Mölle, M. (2013) Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. *Neuron* 78, 545–53.
- (76) Fuermaier, A. B., Tucha, L., Koerts, J., van Heuvelen, M. J., van der Zee, E. A., Lange, K. W., and Tucha, O. (2014) Good vibrations—effects of whole body vibration on attention in healthy individuals and individuals with ADHD. *PLoS One* 9, No. e90747.
- (77) Trenado, C., Mikulić, A., Manjarrez, E., Mendez-Balbuena, I., Schulte-Mönting, J., Huehe, F., Hepp-Reymond, M. C., and Kristeva, R. (2014) Broad-band Gaussian noise is most effective in improving motor performance and is most pleasant. *Front. Hum. Neurosci.* 8, 22.
- (78) Trenado, C., Mendez-Balbuena, I., Manjarrez, E., Huehe, F., Schulte-Mönting, J., Feige, B., Hepp-Reymond, M., and Kristeva, R. (2014) Enhanced corticomuscular coherence by external stochastic noise. *Front. Hum. Neurosci.* 8, 325.
- (79) Gruzelier, J. H. (2014) EEG-neurofeedback for optimizing performance. I: a review of cognitive and affective outcome in healthy participants. *Neurosci. Biobehav. Rev.* 44, 124–141.
- (80) Escolano, C., Olivan, B., Lopez-del-Hoyo, Y., Garcia-Campayo, J., and Minguez, J. (2012) Double-blind single-session neurofeedback training in upper-alpha for cognitive enhancement of healthy subjects. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2012, 4643–7.
- (81) Escolano, C., Aguilar, M., and Minguez, J. (2011) EEG-based upper alpha neurofeedback training improves working memory performance. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2011, 2327–30.
- (82) Zoefel, B., Huster, R. J., and Herrmann, C. S. (2011) Neurofeedback training of the upper alpha frequency band in EEG improves cognitive performance. *NeuroImage* 54, 1427–31.
- (83) Ochs, L. (2006) The Low Energy Neurofeedback System (LENS): Theory, background, and introduction. *J. Neurotherapy* 10 (2–3), 5–39.
- (84) deBettencourt, M. T., Cohen, J. D., Lee, R. F., Norman, K. A., and Turk-Browne, N. B. (2015) Closed-loop training of attention with real-time brain imaging. *Nat. Neurosci.* 18, 470–475.
- (85) Hohenfeld, C., Nellesen, N., Dogan, I., Kuhn, H., Müller, C., Papa, F., Ketteler, S., Goebel, R., Heinecke, A., Shah, N. J., Schulz, J. B., Reske, M., and Reetz, K. (2017) Cognitive Improvement and Brain Changes after Real-Time Functional MRI Neurofeedback Training in Healthy Elderly and Prodromal Alzheimer's Disease. *Front. Neurol.* 8, 384.
- (86) Clowes, R. (2015) Thinking in the Cloud: The Cognitive Incorporation of Cloud-Based Technology. *Philosophy & Technology* 28, 261–296.
- (87) Brennkneijer, J., and Zwart, H. (2017) From 'Hard' Neuro-Tools to 'Soft' Neuro-Toys? Refocussing the Neuro-Enhancement Debate. *Neuroethics* 10, 337–348.
- (88) Warwick, K. (2014) The Cyborg Revolution. *NanoEthics* 8, 263–273.
- (89) Warwick, K. (2014) A tour of some brain/neuronal–computer interfaces. Brain-Computer-Interfaces in their ethical, social and cultural contexts. *International Library of Ethics, Law and Technology* 12, 131–145.
- (90) Hampson, R. E., Song, D., Robinson, B. S., Fetterhoff, D., Dakos, A. S., Roeder, B. M., She, X., Wicks, R. T., Witcher, M. R., Couture, D. E., Laxton, A. W., Munger-Clary, H., Popli, G., Sollman, M. J., Whitlow, C. T., Marmarelis, V. Z., Berger, T. W., and Deadwyler, S. A. (2018) Developing a hippocampal neural prosthetic to facilitate human memory encoding and recall. *J. Neural Eng.* 15, 036014.
- (91) Burke, J. F., Merkow, M. B., Jacobs, J., Kahana, M. J., and Zaghoul, K. A. (2015) Brain computer interface to enhance episodic memory in human participants. *Front. Hum. Neurosci.* 8, 1055.
- (92) Steinert, S., Bublitz, C., Jox, R., and Friedrich, O. (2018) Doing things with thoughts. *Philos. Technol.*
- (93) Feld, G. B., and Diekelmann, S. (2015) Sleep smart-optimizing sleep for declarative learning and memory. *Front. Psychol.* 6, 622.
- (94) Chang, Y. K., Labban, J. D., Gapin, J. I., and Etner, J. L. (2012) The effects of acute exercise on cognitive performance: a meta-analysis. *Brain Res.* 1453, 87–101.
- (95) Roig, M., Nordbrandt, S., Geertsens, S. S., and Nielsen, J. B. (2013) The effects of cardiovascular exercise on human memory: a review with meta-analysis. *Neurosci. Biobehav. Rev.* 37, 1645–66.
- (96) Hötting, K., and Röder, B. (2013) Beneficial effects of physical exercise on neuroplasticity and cognition. *Neurosci. Biobehav. Rev.* 37, 2243–57.
- (97) Schlaug, G., Norton, A., Overy, K., and Winner, E. (2005) Effects of music training on the child's brain and cognitive development. *Ann. N. Y. Acad. Sci.* 1060, 219–30.
- (98) Seinfeld, S., Figueroa, H., Ortiz-Gil, J., and Sanchez-Vives, M. V. (2013) Effects of music learning and piano practice on cognitive function, mood and quality of life in older adults. *Front. Psychol.* 4, 810.
- (99) Coubard, O. A., Duretz, S., Lefebvre, V., Lapalus, P., and Ferrufino, L. (2011) Practice of contemporary dance improves cognitive flexibility in aging. *Front. Aging Neurosci.* 3, 13.
- (100) Bialystok, E., Craik, F. I., and Luk, G. (2012) Bilingualism: consequences for mind and brain. *Trends Cognit. Sci.* 16, 240–50.
- (101) Worthen, J. B., and Hunt, R. R. (2010) *Mnemonology*, Psychology Press, New York.
- (102) Dresler, M., Shirer, W. R., Konrad, B. N., Müller, N. C. J., Wagner, I. C., Fernández, G., Czigisch, M., and Greicius, M. D. (2017)

Mnemonic Training Reshapes Brain Networks to Support Superior Memory. *Neuron* 93, 1227–1235.

(103) Chiesa, A., Calati, R., and Serretti, A. (2011) Does mindfulness training improve cognitive abilities? A systematic review of neuro-psychological findings. *Clin Psychol Rev* 31, 449–64.

(104) Sedlmeier, P., Eberth, J., Schwarz, M., Zimmermann, D., Haerig, F., Jaeger, S., and Kunze, S. (2012) The psychological effects of meditation: a meta-analysis. *Psychol Bull* 138, 1139–71.

(105) Green, C. S., and Bavelier, D. (2012) Learning, attentional control, and action video games. *Curr. Biol* 22, R197–R206.

(106) Kühn, S., Gleich, T., Lorenz, R. C., Lindenberger, U., and Gallinat, J. (2014) Playing Super Mario induces structural brain plasticity: gray matter changes resulting from training with a commercial video game. *Mol. Psychiatry* 19, 265–271.

(107) Lampit, A., Hallock, H., and Valenzuela, M. (2014) Computerized cognitive training in cognitively healthy older adults: a systematic review and meta-analysis of effect modifiers. *PLoS Med* 11, No. e1001756.

(108) Simons, D. J., Boot, W. R., Charness, N., Gathercole, S. E., Chabris, C. F., Hambrick, D. Z., and Stine-Morrow, E. A. (2016) Do "Brain-Training" Programs Work? *Psychol Sci. Public Interest* 17, 103–186.

(109) Melby-Lervåg, M., Redick, T. S., and Hulme, C. (2016) Working Memory Training Does Not Improve Performance on Measures of Intelligence or Other Measures of "Far Transfer": Evidence From a Meta-Analytic Review. *Perspect Psychol Sci* 11, 512–34.

(110) Stojanoski, B., Lyons, K. M., Pearce, A. A. A., and Owen, A. M. (2018) Targeted training: Converging evidence against the transferable benefits of online brain training on cognitive function. *Neuropsychologia* 117, 541–550.

(111) Diekelmann, S. (2014) Sleep for cognitive enhancement. *Front. Syst. Neurosci.* 8, 46.

(112) Rosekind, M. R., Smith, R. M., Miller, D. L., Co, E. L., Gregory, K. B., Webbon, L. L., Gander, P. H., and Lebacqz, J. V. (1995) Alertness management: strategic naps in operational settings. *J. Sleep Res.* 4 (S2), 62–66.

(113) Noack, H., Lövdén, M., and Schmiedek, F. (2014) On the validity and generality of transfer effects in cognitive training research. *Hematol. Cell Ther.* 78, 773–789.

(114) Mehta, M. A., Swainson, R., Ogilvie, A. D., Sahakian, J., and Robbins, T. W. (2001) Improved short-term spatial memory but impaired reversal learning following the dopamine D(2) agonist bromocriptine in human volunteers. *Psychopharmacology (Berl)* 159, 10–20.

(115) Lees, J., Michalopoulou, P. G., Lewis, S. W., Preston, S., Bamford, C., Collier, T., Kalpakidou, A., Wykes, T., Emsley, R., Pandina, G., Kapur, S., and Drake, R. J. (2017) Modafinil and cognitive enhancement in schizophrenia and healthy volunteers: the effects of test battery in a randomised controlled trial. *Psychol. Med.* 47, 2358–2368.

(116) Hurlemann, R., Patin, A., Onur, O. A., Cohen, M. X., Baumgartner, T., Metzler, S., Dziobek, I., Gallinat, J., Wagner, M., Maier, W., and Kendrick, K. M. (2010) Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans. *J. Neurosci.* 30, 4999–5007.

(117) Chini, B., Leonzino, M., Baida, D., and Sala, M. (2014) Learning about oxytocin: pharmacologic and behavioral issues. *Biol. Psychiatry* 76, 360–6.

(118) Fallon, S. J., van der Schaaf, M. E., Ter Huurne, N., and Cools, R. (2017) The Neurocognitive Cost of Enhancing Cognition with Methylphenidate: Improved Distractor Resistance but Impaired Updating. *J. Cogn Neurosci* 29, 652–663.

(119) Takeuchi, H., Taki, Y., Sassa, Y., Hashizume, H., Sekiguchi, A., Fukushima, A., and Kawashima, R. (2011) Working memory training using mental calculation impacts regional gray matter of the frontal and parietal regions. *PLoS One* 6, No. e23175.

(120) Farah, M. J., Illes, J., Cook-Deegan, R., Gardner, H., Kandel, E., King, P., Parens, E., Sahakian, B., and Wolpe, P. R. (2004)

Neurocognitive enhancement: what can we do and what should we do? *Nat. Rev. Neurosci.* 5, 421–5.

(121) Iuculano, T., and Cohen Kadosh, R. (2013) The mental cost of cognitive enhancement. *J. Neurosci.* 33, 4482–6.

(122) Brem, A. K., Fried, P. J., Horvath, J. C., Robertson, E. M., and Pascual-Leone, A. (2014) Is neuroenhancement by noninvasive brain stimulation a net zero-sum proposition? *NeuroImage* 85, 1058–68.

(123) Ilieva, I., Boland, J., and Farah, M. J. (2013) Objective and subjective cognitive enhancing effects of mixed amphetamine salts in healthy people. *Neuropharmacology* 64, 496–505.

(124) Finke, K., Dodds, C. M., Bublak, P., Regenthal, R., Baumann, F., Manly, T., and Müller, U. (2010) Effects of modafinil and methylphenidate on visual attention capacity: a TVA-based study. *Psychopharmacology (Berl)* 210, 317–29.

(125) Chou, H. H., Talledo, J. A., Lamb, S. N., Thompson, W. K., and Swerdlow, N. R. (2013) Amphetamine effects on MATRICS Consensus Cognitive Battery performance in healthy adults. *Psychopharmacology (Berl)* 227, 165–76.

(126) Knott, V., de la Salle, S., Choueiri, J., Impey, D., Smith, D., Smith, M., Beaudry, E., Saghir, S., Ilivitsky, V., and Labelle, A. (2015) Neurocognitive effects of acute choline supplementation in low, medium and high performer healthy volunteers. *Pharmacol., Biochem. Behav.* 131, 119–29.

(127) Yerkes, R. M., and Dodson, J. D. (1908) The relation of strength of stimulus to rapidity of habit-formation. *Journal of Comparative Neurology and Psychology* 18, 459–482.

(128) Duffy, E. (1957) The psychological significance of the concept of "arousal" or "activation." *Psychological Review* 64, 265–275.

(129) de Jongh, R., Bolt, I., Schermer, M., and Olivier, B. (2008) Botox for the brain: enhancement of cognition, mood and pro-social behavior and blunting of unwanted memories. *Neurosci. Biobehav. Rev.* 32, 760–76.

(130) Hills, T., and Hertwig, R. (2011) Why aren't we smarter already: Evolutionary trade-offs and cognitive enhancements. *Current Directions in Psychological Science* 20, 373–377.

(131) Wood, S., Sage, J. R., Shuman, T., and Anagnostaras, S. G. (2014) Psychostimulants and cognition: a continuum of behavioral and cognitive activation. *Pharmacol. Rev.* 66, 193–221.

(132) van der Schaaf, M. E., Fallon, S. J., Ter Huurne, N., Buitelaar, J., and Cools, R. (2013) Working memory capacity predicts effects of methylphenidate on reversal learning. *Neuropsychopharmacology* 38, 2011–2018.

(133) Whitlock, L. A., McLaughlin, A. C., and Allaire, J. C. (2012) Individual differences in response to cognitive training: Using a multi-modal, attentionally demanding game-based intervention for older adults. *Computers in Human Behavior* 28, 1091–1096.

(134) Jaeggi, S. M., Buschkuhl, M., Jonides, J., and Perrig, W. J. (2008) Improving fluid intelligence with training on working memory. *Proc. Natl. Acad. Sci. U. S. A.* 105 (19), 6829–6833.

(135) Santarnecchi, E., Muller, T., Rossi, S., Sarkar, A., Polizzotto, N. R., Rossi, A., and Cohen Kadosh, R. (2016) Individual differences and specificity of prefrontal gamma frequency-tACS on fluid intelligence capabilities. *Cortex* 75, 33–43.

(136) Habich, A., Klöppel, S., Abdulkadir, A., Scheller, E., Nissen, C., and Peter, J. (2017) Anodal tDCS Enhances Verbal Episodic Memory in Initially Low Performers. *Front. Hum. Neurosci.* 11, 542.

(137) Wilhelm, I., Metzkow-Mészáros, M., Knapp, S., and Born, J. (2012) Sleep-dependent consolidation of procedural motor memories in children and adults: the pre-sleep level of performance matters. *Dev Sci.* 15, S06–15.

(138) Fenn, K. M., and Hambrick, D. Z. (2012) Individual differences in working memory capacity predict sleep-dependent memory consolidation (2012). *J. Exp. Psychol. Gen.* 141, 404–410.

(139) Fenn, K. M., and Hambrick, D. Z. (2015) General intelligence predicts memory change across sleep. *Psychon Bull. Rev.* 22, 791–9.

(140) Langbaum, J. B., Rebok, G. W., Bandeen-Roche, K., and Carlson, M. C. (2009) Predicting memory training response patterns: results from ACTIVE. *J. Gerontol., Ser. B* 64, 14–23.

- (141) Verhaeghen, P., and Marcoen, A. (1996) On the mechanisms of plasticity in young and older adults after instruction in the method of loci: evidence for an amplification model. *Psychol Aging* 11, 164–78.
- (142) Isbell, E., Stevens, C., Pakulak, E., Hampton Wray, A., Bell, T. A., and Neville, H. J. (2017) Neuroplasticity of selective attention: Research foundations and preliminary evidence for a gene by intervention interaction. *Proc. Natl. Acad. Sci. U. S. A.* 114, 9247–9254.
- (143) Gvirts, H. Z., Mayseless, N., Segev, A., Lewis, D. Y., Feffer, K., Barnea, Y., Bloch, Y., and Shamay-Tsoory, S. G. (2017) Novelty-seeking trait predicts the effect of methylphenidate on creativity. *J. Psychopharmacol.* 31, 599–605.
- (144) Genzel, L., Kiefer, T., Renner, L., Wehrle, R., Kluge, M., Grözinger, M., Steiger, A., and Dresler, M. (2012) Sex and modulatory menstrual cycle effects on sleep related memory consolidation. *Psychoneuroendocrinology* 37, 987–98.
- (145) Okagaki, L., and Frensch, P. A. (1994) Effects of video game playing on measures of spatial performance: Gender effects in late adolescence. *J. Appl. Dev Psychol* 15, 33–58.
- (146) Feng, J., Spence, I., and Pratt, J. (2007) Playing an action video game reduces gender differences in spatial cognition. *Psychol Sci.* 18, 850–5.
- (147) Genzel, L., Bäurle, A., Potyka, A., Wehrle, R., Adamczyk, M., Friess, E., Steiger, A., and Dresler, M. (2015) Diminished nap effects on memory consolidation are seen under oral contraceptive use. *Neuropsychobiology* 70, 253–61.
- (148) Dresler, M., Genzel, L., Kluge, M., Schüssler, P., Weber, F., Rosenhagen, M., and Steiger, A. (2010) Off-line memory consolidation impairments in multiple sclerosis patients receiving high-dose corticosteroid treatment mirror consolidation impairments in depression. *Psychoneuroendocrinology* 35, 1194–202.
- (149) Krause, B., and Cohen Kadosh, R. (2014) Not all brains are created equal: the relevance of individual differences in responsiveness to transcranial electrical stimulation. *Front. Syst. Neurosci.* 8, 25.
- (150) Smillie, L. D., and Gökçen, E. (2010) Caffeine enhances working memory for extraverts. *Biol. Psychol.* 85, 496–498.
- (151) Pace-Schott, E. F., and Spencer, R. M. (2014) Sleep-dependent memory consolidation in healthy aging and mild cognitive impairment. *Curr. Top. Behav. Neurosci.* 25, 307–30.
- (152) Yesavage, J. A., Sheikh, J. I., Friedman, L., and Tanke, E. (1990) Learning mnemonics: roles of aging and subtle cognitive impairment. *Psychol Aging* 5, 133–137.
- (153) Dresler, M., Kluge, M., Genzel, L., Schüssler, P., and Steiger, A. (2010) Impaired off-line memory consolidation in depression. *Eur. Neuropsychopharmacol.* 20, 553–61.
- (154) Dresler, M., Kluge, M., Pawlowski, M., Schüssler, P., Steiger, A., and Genzel, L. (2011) A double dissociation of memory impairments in major depression. *J. Psychiatr. Res.* 45, 1593–1599.
- (155) Genzel, L., Ali, E., Dresler, M., Steiger, A., and Tesfaye, M. (2011) Sleep-dependent memory consolidation of a new task is inhibited in psychiatric patients. *J. Psychiatr. Res.* 45, 555–60.
- (156) Genzel, L., Dresler, M., Cornu, M., Jäger, E., Konrad, B., Adamczyk, M., Friess, E., Steiger, A., Czisch, M., and Goya-Maldonado, R. (2015) Medial prefrontal-hippocampal connectivity and motor memory consolidation in depression and schizophrenia. *Biol. Psychiatry* 77, 177–86.
- (157) Segretin, M. S., Lipina, S. J., Hermida, M. J., Sheffield, T. D., Nelson, J. M., Espy, K. A., and Colombo, J. A. (2014) Predictors of cognitive enhancement after training in preschoolers from diverse socioeconomic backgrounds. *Front. Psychol.* 5, 205.
- (158) Harris, E., Macpherson, H., Vitetta, L., Kirk, J., Sali, A., and Pipingas, A. (2012) Effects of a multivitamin, mineral and herbal supplement on cognition and blood biomarkers in older men: a randomised, placebo-controlled trial. *Hum. Psychopharmacol.* 27, 370–377.
- (159) Brefczynski-Lewis, J. A., Lutz, A., Schaefer, H. S., Levinson, D. B., and Davidson, R. J. (2007) Neural correlates of attentional expertise in long-term meditation practitioners. *Proc. Natl. Acad. Sci. U. S. A.* 104, 11483–8.
- (160) Reis, J., Schambra, H. M., Cohen, L. G., Buch, E. R., Fritsch, B., Zarahn, E., Celnik, P. A., and Krakauer, J. W. (2009) Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. *Proc. Natl. Acad. Sci. U. S. A.* 106, 1590–5.
- (161) Cohen Kadosh, R., Soskic, S., Iuculano, T., Kanai, R., and Walsh, V. (2010) Modulating neuronal activity produces specific and long-lasting changes in numerical competence. *Curr. Biol.* 20, 2016–2020.
- (162) Wagner, U., Hallschmid, M., Rasch, B., and Born, J. (2006) Brief sleep after learning keeps emotional memories alive for years. *Biol. Psychiatry* 60, 788–790.
- (163) Dresler, M., Shirer, W. R., Konrad, B. N., Müller, N. C. J., Wagner, I. C., Fernández, G., Czisch, M., and Greicius, M. D. (2017) Mnemonic Training Reshapes Brain Networks to Support Superior Memory. *Neuron* 93, 1227.
- (164) Hinrichs, J. V., Ghoneim, M. M., and Mewaldt, S. P. (1984) Diazepam and memory: retrograde facilitation produced by interference reduction. *Psychopharmacology (Berl)* 84, 158–162.
- (165) Mednick, S. C., Cai, D. J., Kanady, J., and Drummond, S. P. (2008) Comparing the benefits of caffeine, naps and placebo on verbal, motor and perceptual memory. *Behav. Brain Res.* 193, 79–86.
- (166) Franke, A. G., Gränsmark, P., Agricola, A., Schühle, K., Rommel, T., Sebastian, A., Balló, H. E., Gorbulev, S., Gerdes, C., Frank, B., Ruckes, C., Tüscher, O., and Lieb, K. (2017) Methylphenidate, modafinil, and caffeine for cognitive enhancement in chess: A double-blind, randomised controlled trial. *Eur. Neuropsychopharmacol.* 27, 248–260.
- (167) Hammond, D. C., and Kirk, L. (2007) Negative effects and the need for standards of practice in neurofeedback. *Biofeedback* 35, 139–145.
- (168) Whitmarsh, S., Uddén, J., Barendregt, H., and Petersson, K. M. (2013) Mindfulness reduces habitual responding based on implicit knowledge: evidence from artificial grammar learning. *Conscious Cogn* 22, 833–845.
- (169) Stillman, C. M., Feldman, H., Wambach, C. G., Howard, J. H., Jr, and Howard, D. V. (2014) Dispositional mindfulness is associated with reduced implicit learning. *Conscious Cogn* 28, 141–150.
- (170) Wilson, B. M., Mickes, L., Stolarz-Fantino, S., Evrard, M., and Fantino, E. (2015) Increased false-memory susceptibility after mindfulness meditation. *Psychol. Sci.* 26, 1567.
- (171) Shiflett, M. W., Rankin, A. Z., Tomaszycki, M. L., and DeVoogd, T. J. (2004) Cannabinoid inhibition improves memory in food-storing birds, but with a cost. *Proc. R. Soc. London, Ser. B* 271, 2043–2048.
- (172) Sandberg, A., and Bostrom, N. (2006) Converging cognitive enhancements. *Ann. N. Y. Acad. Sci.* 1093, 201–227.
- (173) Sarewitz, D., and Karas, T. (2012) Policy implications of technologies for cognitive enhancement. In *Neurotechnology: Premises, Potential and Problems* (Giordano, J., Ed.), pp 267–285, CRC Press, Boca Raton, FL.
- (174) Northrop, R. B. (2017) *Non-Invasive Instrumentation and Measurement in Medical Diagnosis*, CRC Press, Boca Raton, FL.
- (175) Davis, N. J., and van Koningsbruggen, M. G. (2013) "Non-invasive" brain stimulation is not non-invasive. *Front. Syst. Neurosci.* 7, 76.
- (176) Shirota, Y., Hewitt, M., and Paulus, W. (2014) Neuroscientists Do Not Use Non-invasive Brain Stimulation on Themselves for Neural Enhancement. *Brain Stimul* 7, 618–9.
- (177) Maslen, H., Douglas, T., Cohen Kadosh, R., Levy, N., and Savulescu, J. (2014) The regulation of cognitive enhancement devices: extending the medical model. *Journal of Law and the Biosciences* 1, 68–93.
- (178) Wexler, A. (2017) The Social Context of "Do-It-Yourself" Brain Stimulation: Neurohackers, Biohackers, and Lifehackers. *Front. Hum. Neurosci.* 11, 224.
- (179) Urban, K. R., and Gao, W. J. (2013) Methylphenidate and the juvenile brain: enhancement of attention at the expense of cortical plasticity? *Med. Hypotheses* 81, 988–994.

- (180) Urban, K. R., and Gao, W. J. (2014) Performance enhancement at the cost of potential brain plasticity: neural ramifications of nootropic drugs in the healthy developing brain. *Front. Syst. Neurosci.* 8, 38.
- (181) Landolfi, E. (2013) Exercise addiction. *Sports Med.* 43, 111–9.
- (182) Yung, K., Eickhoff, E., Davis, D. L., Klam, W. P., and Doan, A. P. (2015) Internet addiction disorder and problematic use of Google Glass in patient treated at a residential substance abuse treatment program. *Addict Behav.* 41, 58–60.
- (183) Ilieva, I. P., and Farah, M. J. (2013) Enhancement stimulants: perceived motivational and cognitive advantages. *Front. Neurosci.* 7, 198.
- (184) Ilieva, I., Boland, J., and Farah, M. J. (2013) Objective and subjective cognitive enhancing effects of mixed amphetamine salts in healthy people. *Neuropharmacology* 64, 496–505.
- (185) Ullrich, S., de Vries, Y. C., Kühn, S., Repantis, D., Dresler, M., and Ohla, K. (2015) Feeling smart: Effects of caffeine and glucose on cognition, mood and self-judgment. *Physiol. Behav.* 151, 629–37.
- (186) Bubltz, C. (2016) Drugs, enhancements, and rights. Ten points for lawmakers to consider. In *Jotterand/Dubljevic, Cognitive Enhancement: Ethical and Policy Implications in International Perspectives*, Oxford University Press, New York.
- (187) Farah, M. J., Haimm, C., Sankoorikal, G., and Chatterjee, A. (2009) When we enhance cognition with Adderall, do we sacrifice creativity? A preliminary study. *Psychopharmacology* 202, 541–7.
- (188) Nordberg, A. (2015) Patentability of methods of human enhancement. *J. of Intellectual Property Law & Pract* 10, 19–28.
- (189) Bergström, L. S., and Lynöe, N. (2008) Enhancing concentration, mood and memory in healthy individuals: an empirical study of attitudes among general practitioners and the general population. *Scandinavian Journal of Public Health* 36 (5), 532–537.
- (190) Caviola, L., and Faber, N. S. (2015) Pills or push-ups? Effectiveness and public perception of pharmacological and non-pharmacological cognitive enhancement. *Front. Psychol.* 6, 1852.
- (191) Caviola, L., Mannino, A., Savulescu, J., and Faulmüller, N. (2014) Cognitive biases can affect moral intuitions about cognitive enhancement. *Front. Syst. Neurosci.* 8, 195.
- (192) Faulmüller, N., Maslen, H., and de Sio, F. S. (2013) The indirect psychological costs of cognitive enhancement. *Am. J. Bioeth* 13, 45–7.
- (193) Levy, N. Cognitive Enhancement: Defending the Parity Principle. In *Neuro-Interventions and the Law: Regulating Human Mental Capacity* (Vincent, N., Ed.), Oxford University Press, New York (in press).
- (194) Bubltz, J. C., and Merkel, R. (2014) Crimes against minds: on mental manipulations, harms and a human right to mental self-determination. *Criminal Law and Philosophy* 8, 51–77.
- (195) Focquaert, F., and Schermer, M. (2015) Moral enhancement: Do means matter morally? *Neuroethics* 8, 139–151.
- (196) Macer, D. (2012) Ethical consequences of the positive views of enhancement in Asia. *Health Care Anal* 20, 385–97.
- (197) Singhammer, J. (2012) Age and gender specific variations in attitudes to performance enhancing drugs and methods. *Sport Science Review* 21, 29–48.
- (198) Schelle, K. J., Faulmüller, N., Caviola, L., and Hewstone, M. (2014) Attitudes toward pharmacological cognitive enhancement—a review. *Front. Syst. Neurosci.* 8, 53.
- (199) Liakoni, E., Schaub, M. P., Maier, L. J., Glauser, G. V., and Liechti, M. E. (2015) The use of prescription drugs, recreational drugs, and “soft enhancers” for cognitive enhancement among Swiss secondary school students. *PLoS One* 10, No. e0141289.
- (200) Riis, J., Simmons, J. P., and Goodwin, G. P. (2008) Preferences for psychological traits: The reluctance to enhance fundamental traits. *Journal of Consumer Research* 35, 495–508.
- (201) Sabini, J., and Monterosso, J. (2005) Judgments of the fairness of using performance enhancing drugs. *Ethics and Behavior* 15, 81–94.
- (202) Medaglia, J. D., Yaden, D. B., Helion, C., and Haslam, M. (2019) Moral attitudes and willingness to enhance and repair cognition with brain stimulation. *Brain Stimul.* 12, 44.
- (203) Allen, A. L., and Strand, N. K. (2015) Cognitive enhancement and beyond: recommendations from the Bioethics Commission. *Trends Cognit. Sci.* 19, 549–551.
- (204) Pieramico, V., Esposito, R., Cesinaro, S., Frazzini, V., and Sensi, S. L. (2014) Effects of non-pharmacological or pharmacological interventions on cognition and brain plasticity of aging individuals. *Front. Syst. Neurosci.* 8, 153.
- (205) Lucke, J., and Partridge, B. (2013) Towards a smart population: a public health framework for cognitive enhancement. *Neuroethics* 6, 419–427.
- (206) Schleim, S. (2014) Whose well-being? Common conceptions and misconceptions in the enhancement debate. *Front. Syst. Neurosci.* 8, 148.
- (207) McGaugh, J. L., and Roozendaal, B. (2009) Drug enhancement of memory consolidation: historical perspective and neurobiological implications. *Psychopharmacology* 202, 3–14.
- (208) Savulescu, J., and Bostrom, N. (2009) *Human Enhancement*, Oxford University Press, Oxford.
- (209) Adan, A., and Serra-Grabulosa, J. M. (2010) Effects of caffeine and glucose, alone and combined, on cognitive performance. *Hum. Psychopharmacol.* 25, 310–7.
- (210) Gomez-Pinilla, F., Zhuang, Y., Feng, J., Ying, Z., and Fan, G. (2011) Exercise impacts brain-derived neurotrophic factor plasticity by engaging mechanisms of epigenetic regulation. *Eur. J. Neurosci* 33, 383–390.
- (211) Smith, A. M., Spiegler, K. M., Sauce, B., Wass, C. D., Sturzoii, T., and Matzel, L. D. (2013) Voluntary aerobic exercise increases the cognitive enhancing effects of working memory training. *Behav. Brain Res.* 256, 626–35.
- (212) Bejjani, F., Pereira, S. I., Cini, S. A., and Louzada, F. M. (2014) After being challenged by a video game problem, sleep increases the chance to solve it. *PLoS One* 9, No. e84342.
- (213) Looi, C. Y., Duta, M., Brem, A. K., Huber, S., Nuerk, H. C., and Cohen Kadosh, R. (2016) Combining brain stimulation and video game to promote long-term transfer of learning and cognitive enhancement. *Sci. Rep.* 6, 22003.
- (214) Moreau, D., Wang, C. H., Tseng, P., and Juan, C. H. (2015) Blending transcranial direct current stimulations and physical exercise to maximize cognitive improvement. *Front. Psychol.* 6, 678.
- (215) Marshall, L., Helgadottir, H., Molle, M., and Born, J. (2006) Boosting slow oscillations during sleep potentiates memory. *Nature* 444, 610–613.
- (216) Antonenko, D., Diekmann, S., Olsen, C., Born, J., and Mölle, M. (2013) Napping to renew learning capacity: enhanced encoding after stimulation of sleep slow oscillations. *Eur. J. Neurosci* 37, 1142–1151.
- (217) Cappelletti, M., Gessaroli, E., Hithersay, R., Mitolo, M., Didino, D., Kanai, R., Cohen Kadosh, R., and Walsh, V. (2013) Transfer of cognitive training across magnitude dimensions achieved with concurrent brain stimulation of the parietal lobe. *J. Neurosci.* 33, 14899–14907.